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THE PRINCIPLES OF VACCINE THERAPY*

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There is no subject in biologic therapy quite so difficult of evaluation as vaccine therapy and especially in relation to the treatment of disease. A review of the very extensive literature accumulated during the past twenty-five years leaves one greatly confused and with the impression that the attitude of the physician toward vaccine therapy has frequently influenced the results reported. In other words some physicians appear to have secured uniformly good therapeutic effects while others have observed poor and indifferent results with approximately similar vaccines and technic. This psychological factor apparently exerts an important influence among the laity in that those who have great faith in vaccine therapy almost invariably secure better real or imaginary therapeutic results than those who have little or no faith in this form of treatment. This trust is not infrequently justified by the confidence instilled by those physicians whose results are much superior to the average because they have superior knowledge of methods for preparing and administering vaccines.

FIRST PRINCIPLE

This difference in results and opinions refers almost entirely to the use of vaccines in the treatment of disease. In the prevention of certain diseases, notably of smallpox, rabies, typhoid fever, anthrax and diphtheria, methods of active immunization have yielded such uniformly excellent results that there is a remarkable unanimity of opinion on the value of vaccine therapy constituting

* Read at a Symposium on Vaccine Therapy before the Tenth Annual Convention of the American Society of Clinical Pathologists, Philadelphia, Pennsylvania, June 7–9, 1931.

the first principle namely, *that vaccines have proven of more value in the prevention than in the treatment of disease.*

SECOND PRINCIPLE

That vaccines continue to be used in the treatment of disease despite the poor technic and abuses committed in their use during the past twenty-five years indicates that there must be something of real merit in this form of therapy. Within recent years certain distinct improvements in the methods of preparing stock and autogenous vaccines, with special reference to the utilization of the soluble or exogenous products and toxins of micro-organisms and the abandonment of heat for purposes of sterilization, have apparently improved the results of the vaccine treatment of some diseases as compared with those employing the orthodox heat killed suspensions so that the second principle is *that the method of preparing stock and autogenous vaccines appears to have an important bearing upon their therapeutic value.*

THIRD PRINCIPLE

The maximum of specific effects in active immunization depends to a large extent upon incorporating in the vaccine the important organism or organisms of primary infection rather than those of secondary infection and importance. In other words it may make little or no difference how much skill and care are exercised in the preparation of a vaccine, if the correct and important organism or organisms are absent the maximum of specific effects can not be obtained. For this reason the first essential for success consists in accurate bacteriological diagnosis, not only for the proper selection of a stock vaccine but more particularly for the proper preparation of an autogenous vaccine. Therefore the matter of success or failure in the vaccine treatment of disease rests primarily in the hands of the one making the culture with special reference to the choice of medium and the manner or method of securing and culturing the material. For example, cultures from a discharging ear on plain agar may cultivate only staphylococci or diphtheroid bacilli of secondary infection and miss entirely a primary streptococcus or pneumococcus. Under these conditions a vaccine pre-

pared with the greatest skill may be expected to yield at best only some degree of non-specific effect. Ignorance or carelessness in these particulars may defeat the purpose of vaccine therapy at the very outset and for this reason I believe it may be stated as an important third principle *that successful vaccine therapy demands accurate bacteriological diagnosis and especially the employment of proper and acceptable methods for securing the important organism of infection for the preparation of autogenous vaccines.*

FOURTH PRINCIPLE

Owing to the fact that some species of bacteria exist in more or less well defined, immunologically specific strains and especially in pneumococci, streptococci, meningococci, staphylococci, gonococci, typhoid bacilli and possibly others, it would appear as a fourth principle *that well prepared autogenous vaccines are to be preferred to stock vaccines in the treatment of disease.* It would also appear that stock vaccines for prophylactic immunization should be polyvalent whenever evidence indicates the existence of immunologically specific strains. It is true that polyvalent stock vaccines may meet this principle for the treatment of disease but the fact remains that autogenous vaccines are to be preferred from this standpoint and offer the added advantage of freshness of preparation with possible greater vaccinogenic activity.

FIFTH PRINCIPLE

Since available evidence indicates that living bacteria possess the greatest degree of antigenic activity, it would appear as a fifth principle *that, whenever possible, vaccines should be composed of living organisms of reduced or modified virulence or so prepared as to approach this state as nearly as possible.* For example cowpox vaccination against smallpox still stands as the most efficient example of active immunization because a modified, but living, virus is employed. The same is true in Pasteur's original methods for vaccination against rabies and anthrax. Indeed, the only hope for developing a method for immunization against tuberculosis would appear to reside in the use of living vaccines of tubercle bacilli of reduced virulence as employed in recent years by Cal-

mette and Guérin. For obvious reasons living vaccines are of very limited application but I believe that the principle involved is well defined. For this reason vaccines should approach this state as nearly as possible with the minimum of heat and other technical procedures in their preparation.

SIXTH PRINCIPLE

Since it would appear that the soluble exogenous products and toxins of bacteria rank very high in vaccinogenic activity, I believe that it may be stated as a sixth principle *that these toxins with or without modification should be always incorporated or used whenever possible in the preparation of vaccines.* As examples may be mentioned the notable success of vaccination against diphtheria with toxin-antitoxin and toxoid as well as the measure of success attending vaccination against scarlet fever with the toxin of *Streptococcus scarlatinae* and the greatly improved results in the treatment of staphylococcus infections with the toxins of *Staphylococcus aureus* commonly designated as "filtrates." Furthermore it is well known that the soluble toxins act as the most antigenic agents in the immunization of horses as shown by the success attending the preparation of antitoxins for diphtheria, tetanus, gangrene, scarlet fever, botulinus, and so forth. Since it would appear that the majority of pathogenic organisms are apparently capable of producing some amounts of soluble toxins in fluid culture media of proper hydrogen ion concentration and preparation, it would appear that methods of preparing vaccines should be changed to permit the inclusion of as much toxin as possible.

SEVENTH PRINCIPLE

From this standpoint heat should be used less frequently or abandoned in the sterilization of vaccines and especially in the preparation of staphylococcal vaccines and others in which the toxins are thermolabile. Sterilization with chemical agents like tricresol or phenol appears to produce less destruction of these very desirable vaccinogenic agents so that it may be stated as a seventh principle *that in general terms the sterilization of vaccines with chemical agents or sterilization by filtration are*

to be preferred to sterilization by heat. The method to be employed depends upon the source and nature of the toxin; for example, both heat and chemical agents destroy staphylococcal toxins so that these vaccines are best prepared by filtration alone whereas the vaccinogenic activity of other toxins converted into toxoids by chemical agents appears to be maintained in some degree as in the case of the toxoid of diphtheria toxin. Possibly the best type of vaccine to be employed in the prophylaxis and treatment of disease is that incorporating the soluble toxins along with chemically killed organisms although in the case of diphtheria the toxin alone may be employed because it so nearly constitutes the sole pathogenic agent in the production of this disease.

For several years I have employed vaccines of this kind which may be prepared by cultivating the organism in a suitable broth medium for five days followed by sterilization with tricresol and dilution to the desired numerical strength. In the preparation of staphylococcal vaccines however, in which the action of chemical agents upon toxins is to be avoided, the culture is filtered through a sterile Berkefeld filter and the desired number of separately prepared, chemically killed cocci are added to the filtrate.

Since toxins tend to deteriorate, freshly prepared autogenous vaccines are likely to be more vaccinogenic than stock vaccines of varying age kept at varying temperatures. Furthermore since inflammatory exudates like bronchial secretions are likely to contain soluble toxins, it is to be expected that vaccines composed of the sterile filtrates of such exudates may possess definite vaccinogenic and therapeutic value as indicated by the reports of Eiman and others.

EIGHTH PRINCIPLE

From the standpoint of prophylactic immunization it would appear that results are very largely dependent upon the production of specific antibodies whereas in the treatment of disease certain non-specific effects of therapeutic value may develop so that it may be stated as an eighth principle *that prophylactic immunization is largely dependent upon specific antibody production requiring varying periods of time for the production of adequate*

amounts of antibodies whereas in therapeutic immunization a part of the effect may be more immediate and due in part to non-specific agencies produced by the proteins of the bacteria and culture medium.

NINTH PRINCIPLE

But beyond reasonable doubt the maximal beneficial results possible in prophylactic and therapeutic immunization would appear to be due to antibody production and in this connection the route of administration, dosage and intervals between injections are of importance, especially in the vaccine treatment of disease, and possibly account in part at least for the widely varying results attending vaccine therapy.

From this standpoint the value of the skin as an immunological organ of importance in relation to antibody production commands more attention at present than hitherto and I am disposed to state as a ninth principle *that the intracutaneous injection of vaccines is of more prophylactic and therapeutic value than subcutaneous injections.* At least certain studies by Tuft and others have indicated that more antibody is produced by the former route of administration although the doses must be smaller, but the larger local reactions may constitute an objection to this route of administration. I believe however, that we do well to use intracutaneous injections more frequently than is customary, especially in the treatment of disease. Indeed present and future investigations may show that a particular route of administration may be required for securing the maximal vaccinogenic effects of certain bacteria, the immunizing capacity of pneumococci by oral administration being an example as shown by the recent studies of Ross.

TENTH PRINCIPLE

In this connection Besredka's method of immunization by the local or topical application of vaccines commands a good deal of attention from the standpoint of utilizing the possible antibody producing capacity of the tissues, skin and mucous membranes to a greater extent than is the case when vaccines are given subcutaneously or intramuscularly at a distant focus and on the assumption that antibodies will be produced and conveyed to the infected

tissues by way of the blood or lymph. It is true, however, that the results reported from the use of Besredka's "antivirus" or vaccine by local application may be due to the presence of bacteriophage in the filtrates although I believe that the possibility of therapeutic effects from the local production of antibody is possibly more important than the possible destruction of micro-organisms by bacteriophage, especially if the matter of concentration of the latter is of prime importance as indicated by the recent investigations of Krueger and Northrup.

On the other hand, it would appear that the maximal degree of non-specific effects from vaccines is elicited by intravenous injection in small doses and that second in efficiency is the intramuscular or subcutaneous injection of relatively large doses. For this reason the non-specific protein treatment of disease with stock or autogenous vaccines is best carried out by the intravenous route of administration so that it would appear as a fairly well defined tenth principle *that the route of administration and dosage of vaccines have some bearing upon the results and these should be selected according to the indications and requirements of individual cases.*

It is difficult to furnish definite directions for the administration of vaccines by inexperienced physicians, which constitutes a reason for no small part of the widely varying results observed by physicians in the practice of vaccine therapy and properly accounts for the growing custom of entrusting vaccine therapy to those specializing in this field of therapeutic science.

ELEVENTH PRINCIPLE

There is still such a wide diversity of opinion on the value of vaccines in the treatment of acute bacterial infections that it appears impossible to evolve at present a principle on this phase of the subject. That the administration of a small dose of vaccine materially adds to the burden of toxemia in acute infections can be excluded as a possibility of importance and constitutes an objection of little or no weight. But that the administration of a vaccine in acute infections may result in an over-stimulation of immunological defense is a matter of more importance. Whether the usual assumption that an individual with an acute infection is

undergoing as much immunological stimulation as can be borne or is safe is, however, open to question because of the possibility and probability that antibodies are produced by the tissues directly involved in infection and that the administration of a vaccine may bring into play the immunizing capacities of tissues not otherwise materially involved in antibody production.

My clinical experience has taught me that the administration of small doses of vaccine is frequently of value in the treatment of some acute infections even including the surgical septicemias, so that I believe it may be stated as an eleventh principle *that vaccine therapy is sometimes of value as part of the treatment of acute infections.*

TWELFTH PRINCIPLE

Vaccines probably have their widest field of application in the treatment of chronic infections where the stimulation of antibodies or the production of fever, leukocytosis and other non-specific effects are likely to be of particular value. However, opinion of their value in such cases is subject to great variation and a wide impression prevails that vaccine therapy has not by any means fulfilled original expectations and that the results reported by enthusiasts can not be generally verified or duplicated. So many factors of importance are involved from the method of making the culture for bacteriological diagnosis and securing the right organism or organisms for the preparation of vaccines to the method of preparing and administering them, that it is well to keep an open mind on the subject and pay more attention to ways and means for detecting the reasons and sources of success and failure with proper measures for correcting the latter. Therefore I believe it may be stated as a twelfth and final principle *that vaccines in the treatment of some chronic diseases have met with a measure of success and are worthy of further use especially by those possessing special skill and experience and with due regard for important technical details involving their preparation and administration.*

SUMMARY

In conclusion, these twelve principles may be summarized as follows with the hope that they may arouse renewed interest in vac-

cine therapy and on the assumption that they reflect in a general manner the present status of this important subject:

1. Vaccines have proven of more value in the prevention than in the treatment of disease.

2. Methods of preparation of stock and autogenous vaccines appear to have an important bearing upon their therapeutic value.

3. Successful vaccine therapy demands accurate bacteriological diagnosis, especially the employment of proper and acceptable methods for securing the important organisms of infection for the preparation of autogenous vaccines.

4. Well prepared autogenous vaccines are to be preferred to stock vaccines in the treatment of disease.

5. Whenever possible vaccines should be composed of living organisms of reduced or modified virulence or so prepared as to approach this state as nearly as possible.

6. Bacteriological toxins with or without modification should always be incorporated or used whenever possible in the preparation of vaccines.

7. The sterilization of vaccines with chemical agents or by filtration is to be preferred to sterilization by heat.

8. Prophylactic immunization is largely dependent upon specific antibody production whereas therapeutic immunization is probably due in part to both specific and non-specific effects.

9. The intracutaneous injection of vaccines may be of more prophylactic and therapeutic value than subcutaneous injection.

10. The route of administration and dosage of vaccines have some bearing upon the results and should be selected according to the indications and requirements of individual cases.

11. Vaccine therapy is sometimes of value in the treatment of acute infections.

12. In the treatment of some chronic diseases vaccines have met with a measure of success and are worthy of further use especially by those possessing special skill and experience and with due regard for important technical details involving their preparation and administration.

A CONSIDERATION OF THE THEORETICAL BASES FOR VACCINE THERAPY*

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Any discussion of the subject of vaccines is in danger of becoming prolix by virtue of the diversity of ideas bound up in the word itself. It is in fact noteworthy that whereas in immunology we are plagued and at times confused by the very multiplicity of terms; we have failed to adopt a useful word to substitute for the improperly used vaccine. While at first it might appear that we could do very well with a general understanding that the term vaccine is incorrectly used to cover any antigen used specifically and parenterally for the purpose of conferring immunity, it is consistent with such a procedure to include toxins in such a category and to exclude such agents as Besredka's antivirus. It would appear then that one of the contributions of this symposium might well be an attempt to provide a satisfactory substitute for the word vaccine.

In view of the laxity of the terminology, it is necessary to introduce this paper with the statement that it is concerned only with the prophylactic and therapeutic use of killed bacterial antigens when administered parenterally.

In looking over the literature on this subject, one is struck by the observation that the theory of vaccination practically ceased to develop after the work of Wright and Douglas on opsonins. Since the early days of the century, practically the only justification for the practice of vaccination has been clinical or statistical in nature. Had clinical experience been uniformly favorable, had statistics been unchallenged, and had immunology as a science

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ceased to develop there would be no occasion to do more than to set aside this time in which to eulogize vaccines. If on the other hand theory has lagged, clinical experience failed or statistical evidence faltered, there would be occasion to take account of stock. The fact that we are met is indication that one or all of these situations exists.

The theory of vaccination is essentially this: that parenteral introduction of killed bacterial antigens induces the formation of specific antibodies which in turn neutralize or combat present or succeeding infections with bacteria of the type used in the vaccines. The antibodies involved are agglutinins, precipitins, opsonins, complement fixing and bactericidal antibodies, and to a limited extent antitoxins. If there are others, they are more or less obscure and limited in application. It is essential in evaluating vaccines that we accept this theory, advance another or fall back upon clinical and statistical observations as the sole support for our practices. It is my purpose to indicate the extent to which theory has suffered as a result of modern research in both bacteriology and immunology. This can be accomplished in two ways; first, by considering the ability of specified antigens to produce suitable antibodies in vivo, and second, by appreciating the probable rôle of these antibodies in preventing and removing infection.

That a given killed organism can produce all of the antibodies mentioned above is conceded, and so long as only quantitative differences in separate antibodies could be observed, it was logical to conclude that the antibody thus produced could react with the antigen in the form of the living bacillus. If, however, we permit ourselves any doubt as to the essential identity of the two antigens (living or killed) or if the possibility arises that the agent of infection is different from the organism used as a vaccine, a marked change in procedure is indicated.

While there is and will be for a long time much controversy concerning the extent and significance of so-called bacterial variations or dissociations, there is a general acceptance of some of the more obvious features. For example, it is now recognized that many if not all organisms contain at least a dual antigen. Weil

and Felix[13] were the first to observe the duality of antigen in a single organism. Working with Proteus X 19 and blood from typhus patients they observed qualitative differences in agglutination reactions. They observed that the proteus strain was made up of two antigens, one heat stable, the other heat labile; one produced agglutinins giving a heavy flocculent precipitate, the other agglutinated in fine, slowly settling particles. Felix[3] extended this work by showing that other organisms possessed these two antigens. He went further and claimed that the natural disease (typhoid fever) resulted in the formation of fine agglutinins, whereas inoculation with heat killed antigens produced only the large flaking agglutinins. From this Felix argued that immunization as now practiced has no preventive power since it does not produce reactions equivalent to those resulting from the natural infection.

The fundamental observations of Felix have been amply confirmed although his claims concerning the futility of vaccination have certainly not affected vaccination procedures.

Investigations in the field of microbic dissociation are no less interesting and suggestive. In spite of the extreme claims of certain bacteriologists, there has emerged from studies of the variability of microörganism certain well defined and largely accepted concepts. Among these are the following:

Bacteria are capable of variation within limits characterized by two extreme forms, the so-called S and R types. The S or smooth form is associated with infection, is characterized by maximum virulence and is identified by its smooth, regular colony (with certain exceptions). The R or rough form is obtained by prolonged culture on artificial media or under unfavorable conditions. It is avirulent or has a reduced virulence and grows in a peculiar irregular granular colony. Of greatest interest from the standpoint of vaccination is the behavior of these types when grown in serum produced by the opposite type. Soule[12], Hadley[7] and others have shown that the rough avirulent organism when grown in an antiserum produced by the smooth virulent form becomes itself smooth.

Having confirmed these observations, I[9] investigated the cul-

tures used in the preparation of typhoid vaccine in several leading laboratories and found that in general an R type predominated. The danger of producing sera in inoculated individuals capable of changing avirulent into virulent organisms is obvious. Some time later Grinnell[6] studied the bactericidal power of blood obtained after immunization with smooth and rough strains. He concluded that if bactericidal power of the blood had any value as a measure of immunity, it was decidedly necessary to use a smooth type organism in preparing vaccines. These observations have already had their effect upon routine procedure in the production of vaccines.

The effect on the theory of vaccination of these developments in bacteriology, although seemingly slight, is in fact considerable. So long as there existed only a vague idea that all members of a given bacterial species might not be alike, there was little reason for altering either ideas or practices. As soon, however, as it was definitely shown that bacteria were not only different at varying periods of growth, but that bacterial antigens were materially altered in the process of vitiation, the idea that antibodies resulting from inoculation of killed bacteria were identical with those resulting from infection could not be sustained.

The case for autogenous vaccines is materially strengthened by these observations for here at least antigens are most likely to be of the S type. But this advantage is reduced by using heat to kill the organisms. In fact any process that results in a denaturization of the bacterial proteins must now be regarded with suspicion. Realization of this fact has helped in the development of such substances as antivirus, bacteriophage, and immunogens, vaccines supposedly containing the bacterial proteins in their native state.

The effect of these advances in knowledge of the antigenic structure of bacteria on the theory of vaccination is somewhat devastating. If it can no longer be assumed that the antibodies produced by heat killed vaccines are identical with those produced by living organisms, we are tempted to discount the rôle of antibodies in immunity. This, as a matter of fact, we have been doing for several years.

There are few if any modern immunologists who believe that agglutinins and precipitins play any significant rôle in immunity. The same cannot be said for the opsonins and bactericidal antibodies. It is well known that blood has bactericidal properties and that the leukocytes have power to ingest bacteria. It is not at all difficult to believe that both of these abilities are factors in immunity. So far, however, I have not succeeded in finding studies showing an increase in these so-called antibodies during recovery from disease. It has been demonstrated that bacteriolysins and opsonins are decreased during an acute attack and it appears that following recovery they return to the level generally considered normal. So far as bacteriolysins are concerned, experience has shown that vaccines do not cause them to increase. On the other hand, Grinnell's[6] work previously cited would indicate that the difficulty was with the vaccines.

But the opsonins are our chief comfort and they remain today almost the sole theoretical basis for the use of vaccines in spite of the fact that the testing of sera for opsonic power has become almost a lost art. If we are content to rest our case for vaccines, at least so far as theory goes, on the record of opsonic indices, it is quite in keeping with a sceptical mood to examine the records obtained by various means and especially to compare results obtained by the use of the traditional vaccine and by some of the newer substitutes. This field has scarcely been scratched experimentally and the only facts available concern the enormous increases in indices in the presence of bacteriophage. D'Herelle[2] gives figures as high as forty, Smith[11] above thirty, Weiss and Arnold[14] ten. I have recently worked on this problem and although the indices were lower than those mentioned, they were still above those obtained from vaccines. All of these experiments, however, involved only contact of bacteriophage with bacteria and leucocytes. Attempts to produce sera having high opsonic content by immunization with bacteriophage have not given such encouraging results. The significance of this work, it seems to me, lies in the knowledge that high indices are obtainable. It makes such figures as 2.0 or even 2.5 which are about

the best obtainable with vaccines seem little enough as a basis for a popular and widely used method of treatment.

But if faith in antibodies remains undisturbed by such observations, there exist certain facts that constitute a challenge. Besredka[1] has pretty definitely established the existence of immunity without antibody formation and Gay[5] as well as Freedlander and Toomey[4] have not only confirmed his observations but have indicated the true nature of this immunity by demonstrating the function of the clasmatocyte. That such immunity is confined to the cutaneous tissue is suggested by the work of Hoffstadt and her co-workers[8] who demonstrated that agglutinins and complement fixing antibodies are produced by oral vaccination with typhoid bacilli.

If anything was needed further to disabuse our minds of the idea of the ultimate purposefulness of antibodies, it is furnished by the work of Manwarring[10] and others. As a result of their investigations, we are on the point of conceding that antibodies are not formed by the body but are nothing more than altered antigens and that cells although they may assist in the transformation are not essential to it. True this is in no sense a denial of the existence of antibodies, but by transferring the emphasis we eliminate the feeling of the divine purposefulness of these substances and thus remove what after all has been a very important factor in attempts to connect them with immunity.

It thus appears that vaccination whether for therapeutic or prophylactic purposes is based upon a long vulnerable theory which has in the past few years suffered such buffering as to render it practically useless. Certainly it provides no very firm foundation as a basis for present day practice, and we are faced with the necessity of justifying our procedures by other means, namely practical experience, or of changing the theory. Clinical experience is apparently not giving much comfort; new theories do not promise to develop along lines favorable to vaccination as now practiced. Biologic therapy is progressing towards a substitution of products more closely resembling the living intact but attenuated virus for the vaccine as now used.

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THE USE OF STOCK VACCINES AS A NON-SPECIFIC TREATMENT OF RESPIRATORY INFECTIONS IN CHILDREN*

ROY P. FORBES

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Infections of the respiratory tract contribute about three-fourths of the morbidity of childhood, at least in the winter months. Medical science has sought in vain for specific drugs, vaccines, or sera which might prove of value in the reduction of the morbidity and mortality due to respiratory infections. The pediatrician, like the immunologist, has dreamed of that Utopia in which specificity reigns supreme. We have been reluctant to admit that tuberculosis and syphilis cannot be made to yield to a specific treatment just as diphtheria has done. And yet, a glance at mortality and morbidity statistics convinces us that the progress made in the treatment of tuberculosis and syphilis is almost as spectacular as the results achieved in the specific treatment and in the prevention of diphtheria. Sunshine, natural and artificial, mercury, bismuth, arsphenamine, malaria, and typhoid vaccine have all been found to be non-specific agents of unquestioned value. Is it, therefore, unorthodox or heretical to claim for stock mixed respiratory vaccines a certain non-specific value in the treatment of respiratory infections? The actual areas involved in these infections may or may not be of great significance. At any rate, specificity is not to be implied, with the facts now available.

We are probably agreed that the Bordet-Gengou bacillus is the etiologic agent in pertussis. We also admit that an emulsion of Bordet-Gengou bacilli is not effective in preventing whooping cough in exposed cases, but that it has a certain very limited value in the treatment of this disease. This therapeutic value is

* Read before the Tenth Annual Convention of the American Society of Clinical Pathologists, Philadelphia, Pennsylvania, June 7–9, 1931.

dependent upon very large dosage and can probably be duplicated by a vaccine containing no pertussis organisms, according to Herrman[4] and confirmed by my own observations.

We are also agreed that the use of respiratory vaccines for the prevention of colds has not produced results suggestive of specificity, although no less an authority than Kolmer[5] has noted a relative immunity to colds in vaccinated adults. My experience with the stock vaccines used for prophylaxis against colds in a few children has been most disappointing and tends to strengthen my belief that since respiratory infections are not prevented by the use of prophylactic vaccine, whatever benefit is noted following therapeutic usage must be non-specific.

Previous to 1928, I was opposed to the use of stock respiratory vaccines or "cold shots" as commonly termed by the laity. The thought of using stock respiratory vaccines as a therapeutic measure did not occur to me until Dr. Harry L. Baum, an otolaryngologist of my acquaintance, pointed out good results obtained with the vaccine in the treatment of certain subacute and occasionally acute infections of the throat, nose and the nasal accessory sinuses. I was prevailed upon to use a mixed respiratory vaccine in the treatment of similar cases and was agreeably surprised to note excellent results. Most of the children treated during the first year suffered from subacute or chronic rhinopharyngitis associated with antrum infection, and usually exhibited a troublesome bronchial cough. These cases are frequently diagnosed glibly as "broncho-sinusitis," and constitute one of the most difficult problems for either the pediatrician or the otolaryngologist.

Results in this small group of cases were so gratifying that I was encouraged to try the vaccine in acute respiratory infections. An opportunity was soon presented during a seasonal epidemic of so-called influenza in the winter of 1928–1929. The vaccine was used only for such patients as had a relapse accompanied by fever and cough. Relapses in cases of influenza are notoriously frequent and are dreaded more than the initial attack on account of the frequency of complications, especially bronchitis and bronchopneumonia. Careful records were kept in 100 cases and com-

pared with those of 100 control cases of influenza with relapse in which the patient did not receive vaccine. It was found that the vaccine treated patients did not develop chest complications after vaccine was begun, whereas in the control series five children developed either bronchitis or bronchopneumonia while under careful observation and treatment. However, the incidence of other complications, notably otitis and cervical adenitis, was in no way affected by the vaccine therapy. Subsequent experience has repeatedly confirmed this observation, and I never advise the use

TABLE

SUMMARY OF RESULTS OF VACCINE THERAPY IN 250 CHILDREN TREATED DURING AN EIGHTEEN MONTHS PERIOD 1928–1929

Rise in temperature was seldom encountered and not recorded in subacute rhinopharyngitis and subacute bronchitis. The cases of bronchopneumonia were all early cases treated in the home. Results with hospitalized cases of pneumonia are recorded elsewhere.[3]

	NUMBER CASES	AVERAGE AGE	AVERAGE NUMBER INJECTIONS	PERCENTAGE SHOWING TEMP. RISE	PERCENTAGE RESULTS RECORDED AS		
					Good	Fair	Poor
Acute throat infections	67		1.28	46.5	62.8	29.8	7.4
Acute rhinopharyngitis	39	4.8	1.9	55.0	60.0	20.0	20.0
Subacute rhinopharyngitis	13	7.0	3.7		92.3		7.7
Acute laryngitis	27	3.0	1.4	78.0	55.5	40.8	3.7
Acute bronchitis	60			69.0	80.0	18.3	2.7
Subacute bronchitis	8	6.0	3.2		75.0	12.5	12.5
Asthmatic bronchitis	16	3.1	2.1	44.0	55.5	22.2	22.2
Bronchopneumonia	26	3.4	2.1		75.9	24.1	

of vaccine in cases of otitis, mastoiditis, or cervical adenitis except in cases where there is a concomitant cough or bronchitis.

Having convinced myself of the efficacy of vaccine therapy in both upper respiratory and certain acute lower respiratory infections, I did not hesitate to try vaccine therapy for laryngitis also for acute, subacute, and asthmatic bronchitis, and in pneumonia.

It is my impression that vaccine therapy is not indicated for all infections of the upper respiratory tract but only in cases in which cough or nasal discharge is a prominent symptom. Acute, self-limited infections such as tonsillitis or uncomplicated influenza do

not deserve vaccine therapy. Nor do suppurative otitis or acute cervical adenitis yield to it. The most striking results are obtained in cases of acute laryngitis and bronchitis accompanied by fever. A dry, frequent, unproductive cough becomes loose and productive within twenty-four hours after injection and the temperature frequently returns to normal within thirty-six hours. One injection of vaccine is frequently sufficient to terminate an acute infection, but subacute or chronic infections such as subacute rhinopharyngitis and subacute bronchitis usually require from two to four injections at forty-eight hour intervals and with increasing dosage. Febrile reactions are to be anticipated in the acute infections, but are less common and never severe in the subacute or chronic infections. As a corollary to this observation, the dosage of vaccine may be relatively greater in the subacute infections. The tabulation summarizes some of my observations during a period of eighteen months when the vaccine was put on trial and careful observations recorded in each case.

It is desirable to use a heavy bacterial emulsion so that large dosage may be administered in a quantity not exceeding 1 cc. I have been using an emulsion containing 2 billion organisms per cc., the dosage varying from .1 cc. to 1 cc., according to the age and the condition of the patient. Disappointing results may be obtained if an insufficient dosage is administered, especially in severe cases of acute laryngitis or bronchitis where it is hoped that pneumonitis may be aborted by the vaccine. Mild, early cases of bronchopneumonia frequently clear up after one injection. Severe cases require repeated injections and in well advanced pneumonitis the value of the vaccine is questionable. The wheezing and coughing of asthmatic bronchitis are usually promptly relieved by vaccine therapy, but pure asthma not due to infection is not amenable to such treatment.

The criteria for the estimating of results are mentioned elsewhere,[1,2] but it is freely granted that the personal equation greatly influences the interpretation of clinical observations. Having begun this work as a skeptic, it was not difficult to maintain a conservative attitude in the evaluation of results obtained. Surely one does not expect to obtain 100 per cent of good results with a

procedure which is admittedly nonspecific. The average critical physician will not be convinced of the apparent efficacy of vaccine therapy by the results shown in the tabulation. Besides the "personal equation" he finds other unstable components in such a clinical report, such as chance, too small a number of cases, and that ephemeral but powerful factor called by Brenneman the "vis medicatrix naturae."

Far more convincing than tabulated results are two observations which have resulted from these studies; first, that parents have frequently requested the administration of the vaccine for subsequent respiratory infections, and second, that other pediatricians in Denver have begun to use stock respiratory vaccines and found them to be of value.

No discussion of vaccine therapy would be fair or complete without pointing out the disadvantages of such therapy. Such disadvantages are by no means unimportant. The physician does not wish to risk losing the confidence of a child or parent by needle therapy of any kind. It is essential that the smallest sized hypodermic needle be used and that the physician exhibit at once a certain dexterity of both fingers and tongue, talents to be acquired from the prestidigitators of the stage. The local reaction is generally painful for twenty-four hours and not conducive to inviting repeated injections, even though an excellent result is obtained with the first injection. The systemic reaction, sometimes with high temperature for a few hours, is even less apt to inspire confidence in the physician. It is indeed unfortunate that these undesirable local and systemic reactions cannot be avoided. A preparation known as Omniodol containing bacterial products of value for non-specific therapy does not cause severe local or systemic reactions. This product enjoys some popularity in European clinics, but it is expensive and inconvenient to use. I have had insufficient experience with the preparation to say whether it can be substituted for mixed respiratory vaccine. Finally, the physician using vaccines at the present time runs the risk of labeling himself as a faddist, or at least as being out of step with the profession.

In conclusion, my own experience based on the use of stock respiratory vaccines in approximately 1,000 cases leads me to be-

lieve that this form of non-specific therapy has a definite value in the treatment of certain respiratory infections, and that such value generally outweighs the obvious disadvantages.

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THE ASCHHEIM-ZONDEK PREGNANCY TEST

Its Clinical Application in a series of Cases*

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The need of a satisfactory laboratory test for pregnancy has long been recognized, but the great majority of those which have been introduced have failed to satisfy the requirements for such a laboratory procedure. One of the most outstanding developments in the field of laboratory diagnosis within the past few years has been the Aschheim-Zondek reaction for the diagnosis of pregnancy. This test depends for its value on a sound scientific principle, and is comparatively simple to perform.

Smith and Engle,[4] and Zondek and Aschheim,[5] independently and practically simultaneously, found that a hormone of the anterior pituitary gland has the property of stimulating the reproductive system. It is not specific for either sex, and stimulates alike the ovaries of the female, and the testes of the male. This hormone when injected into immature animals causes a premature maturity, with the establishment of the active reproductive function.

Aschheim and Zondek[1, 2] found, with rare exceptions, that in no condition except pregnancy was there an abundance of the anterior pituitary hormone secreted; but in pregnancy large amounts were liberated and excreted in the urine. The test is based on the above facts.

The technic of the test is quite simple, and requires no particular skill either in operation or interpretation. Two points how-

* We wish to express our appreciation to the many physicians who have aided us with specimens, clinical data and criticisms, and particularly to Dr. C. B. Ingraham, Professor of Obstetrics and Gynecology, University of Colorado School of Medicine and Hospitals.

ever must be kept in mind: first, the age of the animals, which in the case of mice must not be less than twenty-one nor more than twenty-five days at the start of the test. When rats are used they must not be less than twenty-eight nor more than thirty-five days of age at the start of the test, second, the full number of injections must be given at regular intervals, and the animals must be killed at a definite time after the first injection, ninety-six to one hundred hours for mice, and one hundred and ten to one hundred and twenty hours for rats.

The first specimen of urine of the morning voided in a clean receptacle after careful cleansing of the parts is satisfactory, although a catheterized specimen is more desirable. The specimen is preserved by the addition of a small amount of toluol, and is kept in an ice box. This prevents the loss of animals due to bacterial contamination of the specimen. The hormone is found to be thermolabile (56°C.), and does not readily pass through a Berkefeld filter. For these reasons urinary specimens cannot be sterilized by heat or filtration. The technic as will be described is modified slightly from that of the original workers, and has proven satisfactory.

Young immature female white rats from twenty-eight to thirty-five days old are used. At least two animals are employed for each specimen of urine. Injections of 1.5 cc. of urine are made subcutaneously three times a day, for three consecutive days. One hundred and twenty hours after the first injection the animals are killed, and the ovaries examined macroscopically. The original technic consists of six injections in young female mice over a period of two days, and the animals are sacrificed ninety-six hours after the first injection.

The presence of enlarged ovaries with numerous blood points constitutes a positive test, and the macroscopic examination is sufficient for practical interpretation. These ovaries when sectioned will show numerous developing corpora lutea, many of which are in the stage of the corpora hemorrhagia. There is also marked congestion of the ovary, and this with the corpora hemorrhagica gives the macroscopic picture as mentioned above. In most cases rupture of the follicle has not taken place. The ovum

is contained within the developing corpora lutea, corpora lutea atretica.

A negative test shows the ovaries unchanged, or slightly enlarged, with no blood points present. Corpora hemorrhagica or corpora lutea are not seen on microscopic examination, but there may be some follicular development.

Frequently, there is present in the urine of women a considerable amount of ovarian hormone. This hormone will cause the enlargement and maturation of the genitalia of the test animals, with the exception of the ovaries. This same enlargement and maturation also occurs when urine which contains anterior pituitary hormone is injected, due to the production of ovarian hormone in the ovaries of the test animal. Thus it is evident that the interpretation of the test must be based on the changes in the ovary, rather than on the changes in the rest of the genitalia.

Any test to be of clinical value must give a positive reaction early in pregnancy, before physical signs are present. Aschheim and Zondek,[2] and others have reported satisfactory results on early cases, and the first workers stated that the hormone is more abundant early in pregnancy than during the latter months.

Practical use of the test has been made on suspected cases in the hospitals and out-patient department of this institution, also on cases referred by physicians. All cases were followed to delivery, or until definitely proven pregnant, or not pregnant clinically. In the series of cases tested, the majority were early pregnancies and non-pregnant conditions suggestive of pregnancy. In addition, a small number of cases of pregnancy in the later months were run. A moderate number of cases not concerned with pregnancy were also tested, in an attempt to find some other condition which might cause the same reaction as pregnancy. A small series of urine specimens from males proved so consistently negative that they were discontinued.

Occasional reactions are encountered which cannot be read as definitely positive or negative. The test is repeated in these cases with a fresh urinary specimen before a final report is made.

The tabulation shows that in this series false positive reactions are the more common. A brief summary of a case in error may be of interest.

Mrs. C., aged thirty-seven years, white, weight two hundred and ninety-six pounds. On March 25, 1930, patient stated she had missed one period. Examination was not satisfactory on this date. An Aschheim-Zondek test was run on a specimen of urine collected at this time and gave a doubtful result. A second test was run on a specimen of urine obtained April 8, 1930. Ovaries of the test animals were normal. Reported negative. May 8, 1930, vaginal examination showed a firm cervix, probably no pregnancy. A third test was run on a specimen of urine obtained at this time. Ovaries of the test animals were enlarged and quite hemorrhagic, and were reported as positive. On July 12, 1930, patient entered hospital complaining of bleeding from the vagina, nausea, and pains in lower abdomen and back. There was a history of three pregnancies resulting in abortions. Diagnosis of threatened abortion was made. Bleeding and pains ceased on the second day and patient was discharged on July 17, 1930. October 10, 1930, no evidence of pregnancy could be found on examination and roentgenogram of the abdomen was negative for pregnancy.

TABLE

RESULTS WITH MODIFIED ASCHHEIM-ZONDEK TEST

	POSITIVE REACTIONS	NEGATIVE REACTIONS	PER CENT ERROR
Cases of pregnancy:			
Less than three months	90	1	1.1
Three to six months	37	1	2.63
Six months to term	17	0	0.0
Total	144	2	1.37
Non-pregnant cases:			
Males	0	34	0.0
Females	4	71	5.33
Total	4	105	3.67
Total error in 255 cases			2.35

This case may have had a missed abortion prior to her hospitalization on July 12, a very likely possibility in view of her previous history.

The following case illustrates very well the early date after conception that the urine may give a positive reaction.

Mrs. M., (Courtesy of Dr. G. C. Main), aged thirty, white. Husband was home over night for first time in six weeks. Patient should have menstruated three days later but did not. Test was run ten days after coitus. Ovaries of the test animals were large and hemorrhagic, a positive reaction. Patient aborted one month after coitus, and the products of conception were shown to her physician who estimated them to be of not more than one month's duration.

The great similarity between the ovaries of young animals injected with urine from a case of pregnancy and the ovaries of young animals which have received anterior pituitary transplants is rather conclusive evidence that the test demonstrates the presence or absence of the anterior pituitary hormone. This hormone is sex nonspecific, since in addition to the ovarian changes seen in young female rats, the immature males will show testicular enlargement and maturity of external genitalia when given anterior pituitary transplants, or injected with urine from a case of pregnancy.[3] These facts substantiate the statement of German workers that the anterior pituitary hormone is the motor hormone of the reproductive system.

Young males may be used for the test, but they are not so satisfactory as the young female animals, since the results are not so clear cut, and the former require a longer time interval to develop the characteristic changes.

SUMMARY

The test has given this laboratory a very satisfactory means for the differential diagnosis of early pregnancy, since the low percentage of error ranks it with the most accurate of laboratory procedures. In many cases very definite and valuable aid has been given the clinician in the diagnosis of the presence or absence of pregnancy at a time when the clinical signs were of little or no help.

The use of rats in place of mice has proven very satisfactory, for several reasons. The rats are larger, mature later, and so can be used when older and better able to withstand infection. The mortality in these test animals is practically nil as compared with

the large number lost when mice are used. It is also much easier to handle the larger animals, and to read the results macroscopically.

Toluol as a preservative of the urinary specimens has proven very satisfactory, since it in no way effects the hormone content of the urine and does keep down the bacterial contamination. By its use specimens may be sent from a considerable distance, and run at a central laboratory. Specimens a week to ten days old preserved with toluol have been tested and have given accurate results.

The results as obtained by the procedure used in this series have failed to show any material difference in the quantity of hormone early or late in pregnancy. They do show that the hormone is demonstrable very early in pregnancy, which makes the test satisfactory as an early diagnostic aid.

Modifications with the use of rabbits offer a shortened time interval, but for routine tests white rats have proven more economical, require less technical skill, and the time element, with rare exceptions, has been negligible.

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RECURRENT AGRANULOCYTOSIS

Report of an Unusual Case

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Agranulocytosis has come to be recognized as a clinical entity that has a definite pathology, as a disease that is dramatic in its onset and course and usually fatal in its outcome. Though the cause of the disease remains unknown at this time, much evidence has accumulated to shed light on the course of events and pathological picture.

The case report in this paper is of unusual interest because of the recurrent acute attacks interspersed with prolonged periods of chronic granulopenia, the possible association with previous administration of typhoid vaccine, and the coincidence of a severe methemoglobinemia. It is also of interest because of the recorded blood counts during these periods, by means of which further evidence is afforded that the onset in the bone marrow precedes the appearance of clinical symptoms.

CASE REPORT*

The patient, white, aged forty-four years, was a housewife with four healthy children, and lived under good economic conditions.

Her history included bilateral salpingitis in 1915, bilateral otitis media following scarlet fever in 1918, with a partial deafness since that time. She had always been subject to frequent attacks of colds and conditions diagnosed as influenza. She has had a large number of courses of various types of vaccine therapy during the previous ten years, including catarrhalis mixed vaccine three times, typhoid vaccine three times, and mixed pneumococcus vaccine twice, each course consisting of from four to eight subcutaneous doses.

For the previous five years she had complained of periods of weakness, which on some occasions had necessitated her giving up her household duties and

* For the privilege of reporting this case I am indebted to Dr. E. Bates Bloch, Atlanta, Ga.

staying in bed for a few days. No blood counts had been done in those periods. One of her chief complaints was habitual constipation. For five years, she had had a peculiar slate color of skin and mucous membranes, which was later determined to be due to methemoglobinemia. For six months prior to the attacks of agranulocytosis she had been treated for bilateral maxillary sinusitis with little improvement, though the infection was not purulent at any time.

About four weeks prior to the first attack she had received the last of a series of five doses of prophylactic typhoid inoculations, each being followed by a severe reaction, including fever to 103 degrees. She had not been entirely well following the final dose, but had had a mild fever daily for the four weeks following. Because of this, I reported her case before the Fulton County Medical Society, Atlanta, Georgia, as "Agranulocytosis following prophylactic typhoid inoculations," though at this time I am uncertain as to the rôle this played in producing her first attack. Bromberg and Murphy[1] have reported one such instance. However, the effect of typhoid vaccine on the neutrophiles is a disputed question. Cowie and Calhoun[2] state that it is followed by a leukopenia, while Smith[5] states that it is followed by an initial leukocytosis with a mild leukopenia four days later.

I first saw the patient on May 13, 1930. At that time, she had fever of 102 degrees, was in bed, very weak and tired, though she had no pain. Her condition was essentially the same as it had been for the previous four weeks. She was listless and apparently unconcerned with her condition. Physical examination showed a thin, frail, emaciated white woman with a peculiar slate color of the skin and mucous membranes. There were no abnormal findings of the chest or abdomen, nor ulcerations of the mouth or throat.

The white cell count was 900 with no demonstrable neutrophiles. Daily blood counts were begun with the results as shown in the accompanying table. For one week her condition remained about the same, with little apparent change. On May 19, the count fell to a low figure of 470 leukocytes per cu. mm. with no neutrophiles. Her death was predicted during this period. On May 21, she was sent to Emory University Hospital with a white cell count of 930 and 16 per cent neutrophiles. On that date she received a stimulating dose of x-ray to the long bones, with the blood count on the following day being 2600 and 57 per cent neutrophiles. In this instance, I believe the x-ray therapy was of considerable value.

She steadily improved clinically, with less fever daily, was more alert mentally, and received a second dose of x-ray on the 23rd, and a third dose on the 24th of May. On the latter date her red cell count was 4,420,000; on May 26, it had fallen to 1,190,000. This seemed so remarkable that it was rechecked several times with both venous and capillary blood. The red cells then reached a low point of 1,000,000 on May 27. Because of this, she was immediately given a transfusion of 500 cc. of whole blood. In forty-eight hours the count was again found to be more than 5,000,000. I am unable to explain this remarkable

TABLE

SUMMARY OF BLOOD COUNTS

DATE	LEUKOCYTES	NEUTROPHILES	ERYTHROCYTES	HEMOGLOBIN	REMARKS*
		per cent		*per cent*	
5–13–30	900	0	5,300,000	95	
5–13–30	930	0			
5–14–30	660	0			
5–15–30	750	0			
5–15–30	900	8			
5–16–30	950	9			
5–16–30	1,000	12			
5–17–30	740	0			
5–18–30	580	0			
5–19–30	470	0			
5–20–30	1,000	24	5,300,000	95	
5–21–30	930	16			Admitted to hospital
5–22–30	2,600	57			X-ray therapy
5–23–30	800	34	4,580,000	90	X-ray therapy
5–23–30	880	36	4,700,000	90	
5–24–30	1,300	50	4,420,000	85	X-ray therapy
5–26–30	1,400	56	1,190,000	55	
5–27–30	1,600	64	1,040,000	50	X-ray therapy
5–27–30	1,400	70	1,000,000	50	Transfusion
5–28–30	1,440	70	2,220,000	70	
5–29–30	2,200	62	5,130,000	85	
5–30–30	2,400	76	4,470,000	80	
5–31–30	2,000	75	4,900,000	90	
6– 2–30	3,150	76	5,110,000	90	
6– 3–30	2,950	80	4,700,000	85	X-ray therapy
6– 4–30	2,400	79	4,440,000	85	Left hospital
6– 6–30	3,250	84	5,270,000	95	
6–10–30	4,150	80	5,350,000	95	
6–12–30	5,100	83	5,500,000	95	
6–16–30	5,000	79	4,900,000	90	
6–18–30	4,550	76	5,000,000	90	
6–20–30	4,650	72	5,250,000	90	
6–26–30	2,650	58	4,900,000	90	
6–27–30	2,600	60	5,100,000	95	
6–28–30	4,200	70	5,400,000	95	Admitted to hospital
6–30–30	2,900	62	4,850,000	90	Pleuritis with effusion
7– 1–30	2,400	65			
7– 2–30	3,500	71			
7– 3–30	3,700	62			
7– 5–30	3,650	68			
7– 6–30	3,150	62			

TABLE—*Concluded*

DATE	LEUKOCYTES	NEUTROPHILES	ERYTHROCYTES	HEMOGLOBIN	REMARKS*
		per cent		*per cent*	
7- 7-30	2,750	52			
7- 8-30	3,450	61			
7- 9-30	2,500	58	5,000,000	95	
7-10-30	3,350	72			
7-12-30	3,600	62			
7-14-30	3,350	60			
7-16-30	4,000	64	3,350,000	85	Left hospital
7-18-30	3,350	58	5,000,000	90	
7-21-30	2,900	68			
7-28-30	4,800	62			
8- 7-30	5,700	75			
8-14-30	5,850	78			
8-21-30	5,200	74			
8-28-30	4,650	69			Feeling well. Carrying on household duties
10- 3-30	3,150	52			
10-10-30	2,700	46			
10-20-30	900	0			Feeling well. Recent tooth extraction
10-21-30	200	0			Collapse
10-22-30	200	0			Admitted to hospital
10-22-30	150	0			Transfusion
10-23-30	510	0			Death this date

* All blood cultures negative. No evidence of infection at any time.

disturbance of the erythrocytes, though excessive dosage of x-ray should be considered.

She steadily improved and was discharged from the hospital on June 4, with a white cell count of 2400 and 79 per cent. neutrophiles. After her return home it was necessary for her to remain in bed because of weakness. From June 4 to June 28, attempts were made to check her blood count carefully. During this period the count varied between 2000 and 4000 with the neutrophiles about 80 per cent.

On June 28, she developed a right hydrothorax and was readmitted to the hospital. It was interesting that the white count for two days prior to this had fallen from a level of 4500 to about 2500. She remained in the hospital for three weeks, during which time her right thorax was aspirated and a total of 3500 cc. of clear, amber fluid removed on three occasions. During this period the white count fluctuated between 2000 and 4000, with the percentage of neutrophiles about normal. She was discharged on July 16, was weak, but sat up, and felt better than at any time in the previous two months.

The outstanding feature of the course of illness up to this time was the low blood count of 470, followed by recovery. Rosenthal[4] has stressed the point

that counts below 1000 are likely to prove fatal, basing this observation on his series of five fatalities with counts below that figure and five recoveries with counts above that figure.

A period of two and one-half months elapsed from the date of her discharge from the hospital until her re-admission with the third and fatal attack. During this time she was up, feeling well, carrying on her household duties, and was away one month at the beach on a vacation. Ten days prior to the attack the white cell count was 2700 with 46 per cent. neutrophiles. On October 20, the count was 900 with no neutrophiles, although the was feeling as well as usual. Four days before she had had a tooth extracted. On October 21, she collapsed, became profoundly weak and depressed, and went to bed. She stated that she suffered no discomfort, but that she could hardly raise her head from the pillow. Her white cell count on that date was 200 with no neutrophiles. She was admitted to the hospital on October 22, with the white cell count at 150, received a transfusion, and died on the day following, showing no evidence of infection. Apparently she died from the mere absence of the neutrophiles, though some signs of broncho-pneumonia were present just before death. Despite much effort, permission for a post-mortem examination could not be obtained.

DISCUSSION

The leukocytes fell to 470 in the first attack, followed by recovery, which, so far as I am able to determine, is the lowest recorded leukocyte count followed by even temporary recovery of a patient.

In the third attack the patient's white cell count dropped from a low normal of 3000 to 900 with a complete absence of neutrophiles, with the patient showing no ill effects and feeling as well as usual. This observation is similar to that made by Roberts and Kracke[3] in which it was demonstrated that the blood stream changes occurred before evidence of infection was present.

The question of typhoid prophylaxis as a whole or partial cause of the condition in this patient must be considered.

The sudden falling of the leukocyte count from 4600 to 2600 for two days prior to the attack of pleurisy with effusion is significant, and indicates a causal relationship because of loss of neutrophilic resistance.

The association of the condition with methemoglobinemia may be important, since this patient gave a history of using large amounts of coal tar derivatives during the previous three years.

Since it is known that benzene is a powerful leukocytic depressant, and that coal tar derivatives are for the most part altered benzene rings, the possible association should be considered. In this connection it should be noted that coal tar derivatives have had their widest usage since the World War.

This patient had a tooth extracted four days prior to her final attack. Since this has been the history in many of these patients, this phase of the possible etiology should be investigated.

Since the investigation of the possible etiological factors in this field is a tremendous undertaking, it behooves all who have the opportunity of studying these patients to take very careful and painstaking histories in an effort to find a clue that will lead to the detection of a substance that is responsible for the powerful depression of the bone marrow.

CONCLUSIONS

(1) An unusual case of agranulocytosis is reported, which sheds further light on the sequence of events in this disease.

(2) The co-incidence of agranulocytosis and methemoglobinemia is reported.

(3) It is suggested that the probable etiological factor is a rarely used substance containing benzene or one of its derivatives.

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STANDARD NORMALS AND NORMAL RANGES IN HEMATOLOGY*†

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The routine blood count next to urinalysis is the laboratory examination most frequently used in clinical diagnosis. The results of these examinations have always been reported to the clinician in a form which is often difficult to interpret due to lack of uniformity in the value of the figures used as normal. An effort should be made to make the reports more uniform and provide a more definite method for interpreting the results.

The purpose of this paper is to draw attention to certain figures and recommendations appearing in the chapter on hematology in Approved Laboratory Technic by Kolmer and Boerner, which was prepared under the auspices of the American Society of Clinical Pathologists and which is in press. Unless special attention is drawn to them, their significance and general usefulness may be easily overlooked. I refer particularly to the table of Standard Normals and Normal Ranges recommended for use in reporting blood counts and calculating the various indices. It is hoped that they will meet with general approval and that their use will lead to more uniformity in reporting and interpreting blood counts. A better understanding of them can best be reached by a discussion of their application.

It is to be noted that the figures given under Standard Normals (table 1) do not represent normals in the strict sense. The use of average normals of the various authorities would not seem mathematically or scientifically correct, as the average normal

* Read before the Tenth Annual Convention of the American Society of Clinical Pathologists, Philadelphia, Pennsylvania, June 7–9, 1931.

† Contributed under the Diagnostic Clinic Endowment Fund.

blood is no more 100 per cent than the average normal child is 100 per cent normal. In a stricter sense 100 per cent should be the highest a normal individual can obtain without becoming abnormal. Furthermore, if the average figures were used, about one-half of normal individuals rather than the exceptional one would have over 100 per cent. It being impossible to furnish figures applicable to all localities the situation was met by giving

TABLE 1

STANDARD NORMALS AND NORMAL RANGE*

EXAMINATION	STANDARD NORMAL (100 per cent)	NORMAL RANGE
Hemoglobin (male)	17.3 gms. per 100 cc. of blood	14–18 gms. (80–105 per cent per 100 100 cc. of blood
Hemoglobin (female)	17.3 gms. per 100 cc. of blood	12–15.5 gms. (70–90 per cent) per 100 cc. of blood
Erythrocytes (male)	5 million	4.5 to 6 million
Erythrocytes (female)	5 million	4 to 5.5 million
Leukocytes	According to age (see table 2)	4 to 11 thousand
Cell volume (male)	50 cc. per 100 cc. of blood	40 to 50 cc. per 100 m. of blood
Cell volume (female)	50 cc. per 100 cc. of blood	35 to 45 cc. per 100 cc. of blood
Volume per cent (male)	Double the cell volume	80 to 100 per cent
Volume per cent (female)	Double the cell volume	70 to 90 per cent

* These figures are taken from Approved Laboratory Technic by Kolmer and Boerner, D. Appleton & Co., New York, N. Y., 1931.

two sets of figures namely, "Standard Normals" and "Normal Ranges," the former representing figures to be used as 100 per cent whenever results are reported in per cent and for calculating indices. The figures are high enough in the normal range so that only the exceptional will reach 100 per cent. In most instances round numbers were selected to facilitate the calculation of indices.

Acceptance of these standards does not require any change in methods or opinions regarding normal blood findings. It merely

means the reporting of results according to these standards so that reports from all sources will have the same relative value.

The *Normal Ranges* represent as the name indicates, what might be considered as high and low normal findings. This range may not be applicable to all localities or meet the approval of all hematologists and for that reason it is flexible and subject to change, e.g. if anyone disapproves of them he merely has to substitute his own range in terms of standard normals. Further studies of normal blood will give more exact and additional ranges suitable to different localities, races, environment, and so forth. Whatever range is used, it should be expressed in terms of *Standard Normal* so that reports from various sources will be comparable. A better understanding of the use and value of these normals will be obtained by further discussion of each examination.

HEMOGLOBIN

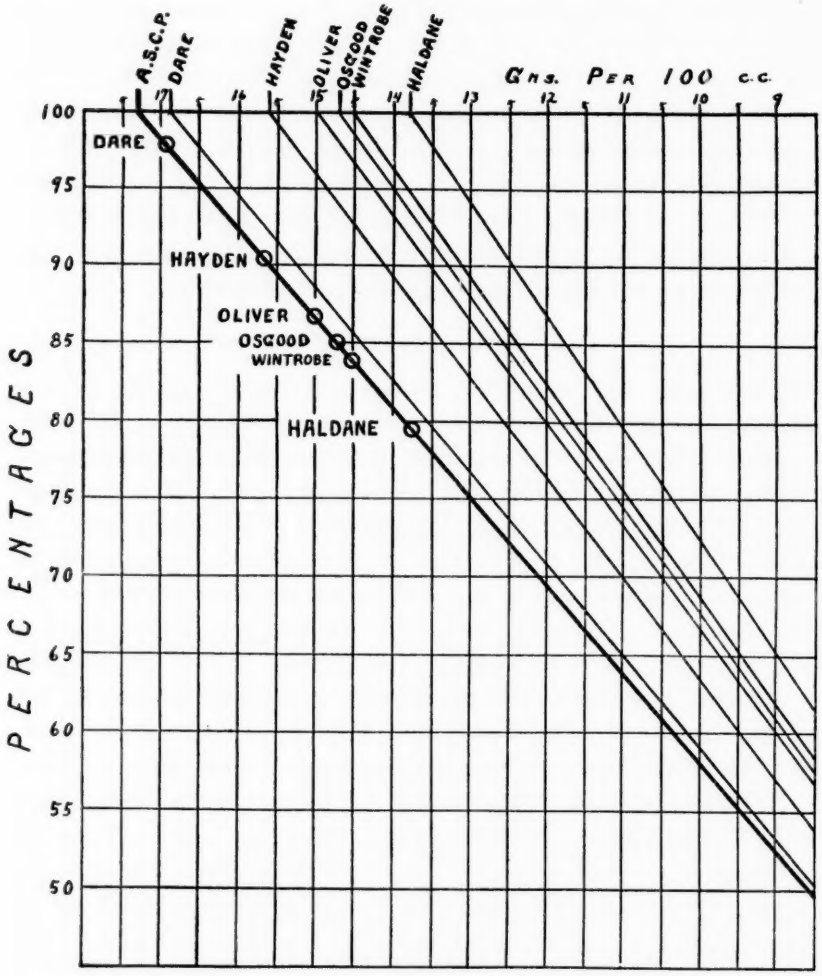
To be exact, 100 per cent normal should represent the largest amount of hemoglobin possible to exist in 100 cc. of normal blood. This would only be found in individuals having the highest normal number of erythrocytes of the largest normal size. Such a figure not being available an approximate figure is given (17.3 grams) which can be used for this purpose without seriously changing the value of the percentages to which the clinician is accustomed.

At present 100 per cent hemoglobin has many values depending upon the scale used for its determination. To overcome this variation and for the sake of uniformity, it has been recommended that the hemoglobin be reported in grams per 100 cc. of blood. This should be given further encouragement and used more generally. However, many laboratories are reporting in percentage due to the clinicians' wish to have it so reported. In such cases if the standard normal of 17.3 is used as 100 per cent there will be but one percentage scale which will represent the same number of grams no matter where the examination is conducted and would tend to uniformity to the same degree as reporting in grams.

By adopting this standard, no one's opinion regarding the average normal or normal range will have to be changed. It merely means that instead of having each authority giving a new value for

100 per cent, they take their position along the line of the percentage scale of the standard normal. The normal range can be decided by the pathologist or clinician to suit his locality.

CHART I*



* The Dare standard of 16.9 gms. was taken from Kilduffe's "Clinical Interpretation of Blood Examinations." The standard has been changed several times by the manufacturers of the instrument and now is said by them to be 16.0 gms.

ERYTHROCYTES (NUMBER)

The figures given are those usually employed for calculating indices and are convenient and suitable for this purpose. They are sufficiently high so that a large majority will fall below 100 per cent although more than the exceptional male will be higher. The same figures are given for both male and female although the ranges vary.

ERYTHROCYTES (VOLUME)

Using 50 per cent as 100 per cent normal for packed cells is convenient for calculating indices and the percentage is sufficiently high so that only the exceptional will be higher. Even though the average normal is closer to 40 than 50 the latter is preferred for reasons stated above. To convert the cell volume per cent into per cent of standard normal it is only necessary to multiply by 2.

INDICES

The use of Standard Normals for calculating the color, volume and saturation index will make the readings uniform and of the same value no matter where they are done.

LEUKOCYTE COUNT

Total count. The total leukocyte count should only be used with the differential count for calculating the actual number of each type of cell per cubic millimeter. To use it alone is the same as weighing a patient to determine if there is an increase or decrease in the size of the organs. The range of 4,150 to 11,050 gives the lowest count possible and the latter the highest with all cells within normal range.

Differential count. The differential count should be used first to determine what per cents of the total are neutrophiles, lymphocytes, and so forth, secondly, to study the red cells and note the presence of abnormal cells, and thirdly, to determine if there is a shift to the left of the neutrophiles (table 2).

Reporting counts. The report of counts should be in compliance with the request of the clinician. He desires to know if there is a

decrease or increase in any of the leukocytes. The custom at the present is to report the total number of cells per cubic millimeter of blood with the percentage of the various types. He looks at the total then at the percentages; some think the total most important and others the percentages. As a result there appears to be a consistent inconsistency in interpreting what should be considered normal or abnormal. The method recommended for overcoming this difficulty is to report the findings in total number of each type of cell, e.g. instead of reporting a total of 12,500 cells with 75 per cent neutrophiles. 23 per cent lymphocytes and 2 per cent monocytes, the report would read—Neutrophiles, 9375, lymphocytes, 2875, monocytes, 250 which would be interpreted

TABLE 2

NORMAL RANGE OF LEUKOCYTES

	3 MONTHS TO 3 YEARS	3 TO 5 YEARS	OVER 5 YEARS AND ADULTS
Neutrophiles	2000–7000	3000–8000	3000–7000
Basophiles	0–50	0–50	0–50
Eosinophiles	25–700	50–700	50–400
Lymphocytes	4000–9000	2500–6000	1000–3000
Monocytes	25–700	25–700	100–600

as a slight neutrophilia. It requires less than a minute to make the necessary calculations. The percentages should only be used as a means to an end and not given as a final answer. The following table which is given in Approved Laboratory Technic of the American Society of Clinical Pathologist can be used for interpreting the findings. Like the normal ranges they can be supplemented and further use of them will no doubt furnish more exact ranges and additional ones particularly for children.

Interpreting the leukocyte count. For simplicity and uniformity the following nomenclature is recommended for reporting abnormal findings in the leukocyte count:

Neutropenia = decrease in polymorphonuclears.
Basopenia = decrease in basophils.
Eosinopenia = decrease in eosinophils.
Lymphopenia = decrease in lymphocytes.

Monopenia	= decrease in monocytes.
Neutrophilia	= increase in polymorphonuclears.
Basophilia	= increase in basophils.
Eosinophilia	= increase in eosinophils.
Lymphocytosis	= increase in lymphocytes.
Monocytosis	= increase in monocytes.

The terms relative and absolute have been omitted as the above terms cover every possible change. A high percentage of

TABLE 3

COMPARATIVE LEUKOCYTE COUNTS USING THE PERCENTAGE AND NUMBER METHOD OF REPORTING

	AUGUST			SEPTEMBER									
	28	29	30	1	2	2	5	6	7	8	9	10	11
Total leukocytes...	3400	2800	1500	450	1500	1100	1400	1300	1000	600	900	450	750
Per cent													
Neutrophiles.....	34	14	29	30	24	18	16	22	12	4	4	20	16
Basophiles.....													
Eosinophiles.....	2	2	1		4	2	4						
Monocytes.....	5	2	1	1				2			8		
Lymphocytes.....	59	82	68	69	72	54	80	76	88	96	88	80	84
Numbers													
Neutrophiles.....	1156	392	435	135	360	198	224	286	120	24	36	90	120
Basophiles.....													
Eosinophiles.....	68	56	15		60	72	140						
Monocytes.....	170	56	15	5				26			72		
Lymphocytes.....	2006	2296	1020	310	1080	880	1120	988	880	576	792	360	630

lymphocytes due to a neutropenia is called a neutropenia and not a relative lymphocytosis, because in the former we state what actually exists and do not involve a type of cell which has not changed from the normal. If the increase percentage is due to an actual increase of lymphocytes, then it is called a lymphocytosis. These terms can be qualified as mild, slight, moderate, marked, and so forth.

To demonstrate further the use and practical value of this method for reporting I would like to present the results of blood

studies in a patient who developed a marked and progressive neutropenia at the Graduate Hospital (table 3).

SUMMARY

By bringing to the attention of the Society the value and purpose of these normal figures, it is hoped that an interest will be stimulated which will lead to their adoption by the members and that measures will be taken to encourage their general use. In conclusion the important points are summarized as follows:

1. The standard normals are not strictly normal, but are figures to be used as standards for reporting blood tests and calculating indices.

2. The normal ranges are what may be considered normal according to standard normal figures. These can be changed to suit the locality or pathologist and are not to be considered standard.

3. The adoption of the standard normal will make all reports of the same value and does not require any change in methods or apparatus.

4. It does not require any change in what was formerly considered normal, except that they will be expressed in terms of standard normal figures.

5. While the pathologists are studying and changing normal ranges, the clinicians will receive reports in uniform values.

6. The use of standard normals does not in any way effect the accuracy of the reports.

7. The interpretation of the reports has to do with the ranges adopted and these can be adjusted to suit the pathologist.

A NEW MODIFICATION OF MALLORY-HEIDENHAIN'S DIFFERENTIAL STAINING METHOD AND ADAPTATION OF FORMALIN-FIXED MATERIAL FOR MALLORY'S STAINS*

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Pathologists are constantly endeavoring to increase their armamentarium to demonstrate better the morbid changes which occur in the tissues of the body. To the histologist, Mallory's stains are invaluable but their uses have been necessarily limited, because tissue to be stained by these methods must be fixed in Zenker's solution. Formalin has become almost the universal fixative because tissue may be preserved in it indefinitely and most stains used as a routine can still be employed. Ever since Mallory described these special methods for Zenker-fixed tissue, histologists have been modifying the fixative and the stains with varying, and usually with unsatisfactory, results. Even washing the tissue and refixing in Zenker's solution is unsatisfactory. Davidoff has suggested placing the formalin-fixed tissue in ammonia water and refixing in Zenker's solution, a procedure which removes some of the difficulties. However, the following adaptation has proved the most satisfactory and uniform method which I have encountered. The formalin-fixed tissues are washed in running water or ammonia water for a short time. The latter procedure serves to prevent the accumulation of "formalin precipitate" on the stained preparation. The tissue is then placed for four days in Weigert's primary mordant for myelin sheaths†

* Read before the Tenth Annual Convention of the American Society of Clinical Pathologists, Philadelphia, Pennsylvania, June 7–9, 1931.

† Weigert's primary mordant for myelin sheaths:

Potassium bichromate	5 gm.
Chromium fluoride	2 gm.
Water	100 cc.

and for two days in Weigert's secondary mordant for myelin sheaths.* It is then embedded in paraffin and stained in the usual way with Mallory's phosphotungstic acid hematoxylin or other staining methods requiring Zenker's fixation. This differ-

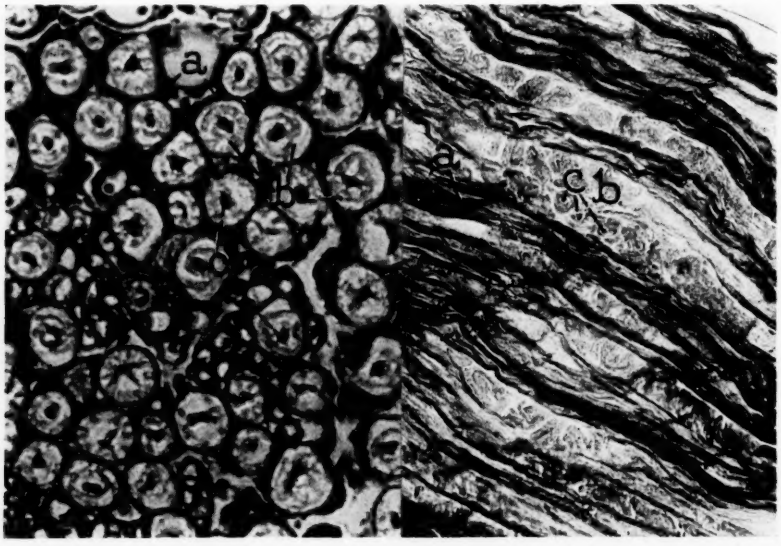

FIG. 1. SECTIONS OF PERIPHERAL NERVES

The left half of the figure is a cross section of a normal sciatic nerve; the nerve was first fixed in formalin and then mordanted with Weigert's myelin sheath mordants; the connective tissue, *a*, is a pale blue and the myelin sheaths, *b*, are red or deep orange; the axis cylinders, *c*, are deep blue or purple (Mallory-Heidenhain's stain ×500). The right half is a longitudinal section of a degenerating femoral nerve; the staining method is the same as in the left section. The connective tissue, *a*, is pale blue; the myelin, *b*, which is breaking down and collecting in masses, is red or deep orange; in the midst of some of the myelin masses are small black clots, *c*, which represent fragments of axis cylinders which stain deep blue or purple (×250).

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* Weigert's secondary mordant for myelin sheaths:

Acetate of copper	5 gm.
Chromium fluoride	2.5 gm.
Acetic acid, 36 per cent	5 cc.
Water	100 cc.
Formalin	10 cc.

entiates the neuroglia, fibroglia, and so forth, as satisfactorily and clearly as if the tissue had been fixed in Zenker's solution, and excellent results have been obtained after the tissue has been fixed several years in formalin. Heidenhain's[1] modification of Mallory's ethyl violet orange G. stain is valuable after Zenker's fixation, and the foregoing modification makes it available after

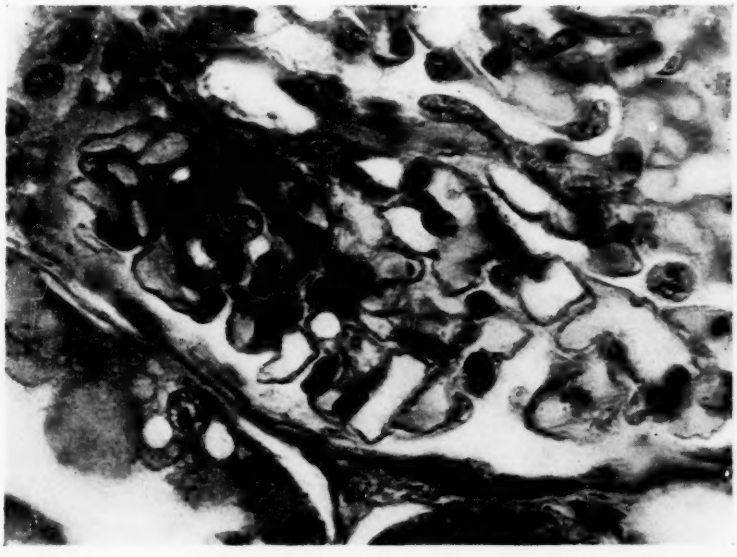

FIG. 2. SECTION THROUGH A GLOMERULUS SHOWING BOWMAN'S CAPSULE AND THE CAPILLARY TUFTS

The connective tissue of the capillaries stains blue and is rendered very prominent with this stain. The basement membrane of the tubules also stains distinctly (Mallory-Heidenhain's stain after fixation in formalin and Weigert's myelin sheath mordants ×720). (After Wilbur.)

fixation in formalin. It is particularly applicable to the peripheral and sympathetic nervous systems. After Weigert's mordant, Weigert's myelin sheath stain may be used, but I have found the Mallory-Heidenhain stain even more valuable, particularly for those nerves in which only slight amounts of myelin are present and from which the hematoxylin so frequently disappears during differentiation. With this stain, the myelin is reddish-orange,

the connective tissue is bright blue and the axis cylinders stain deep blue or purple (fig. 1). Occasionally, in degenerating nerves the axis cylinders are deep red, simulating the reverse reaction of Alzheimer; however, it is not constant. Differentiation is less drastic than with Weigert's myelin sheath stains and consequently smaller amounts of myelin retain the stain and are thus rendered

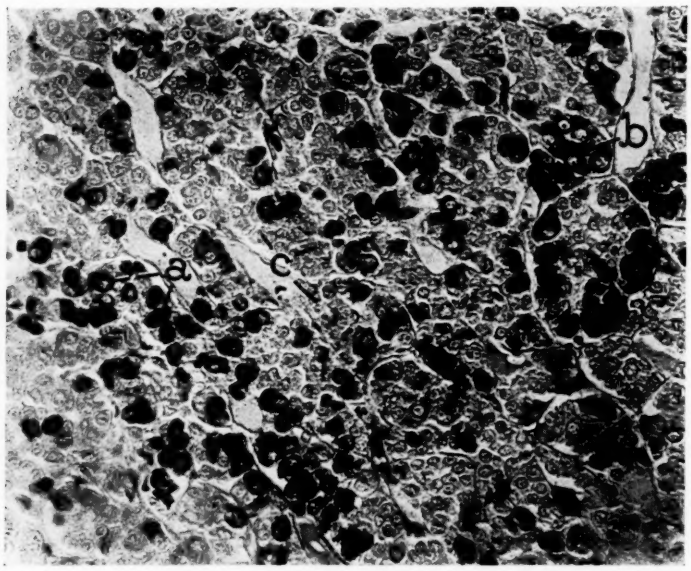

FIG. 3. NORMAL PITUITARY GLAND

With the Mallory-Heidenhain staining method the connective tissue stroma around the blood sinus and so forth, is pale blue. The chromophil cells, *a*, are bright red to orange, depending on the length of time the tissue was in formalin before being cromated. The basophilic cells, *b*, are deep blue or purple, depending on the number of chromophil granules present. The chromophobe cells, *c*, are a pale blue without granules (Mallory-Heidenhain's stain ×300).

visible. This is particularly true in studies of the sympathetic nervous system. The method has a wide application in the field of general pathology and histology and in studies on the glomeruli of the kidney (Heidenhain,[1] McGregor,[2] and others) when differentiation of tissues is important; Wilbur[3] has also found it valuable in this connection (fig. 2). It demonstrates the reticulum

of the liver, spleen, lymph nodes, and so forth, and also the blood vessels in hemangio-endotheliomas and other tumors.

Histologists have endeavored for years to differentiate by stains the three types of cells in the pituitary gland, especially by the use of one stain. After fixation in formalin or with the use of unfixed tissue, when mordanted in Weigert's myelin sheath mordants and Mallory-Heidenhain's or azocarmine stain is used, the three types of cells are clearly contrasted (fig. 3). The chromophil cells are bright red, the chromophobe cells are pale blue and the basophil cells are deep blue or purple and readily distinguished from each other. Many cells contain both chromophil and basophil granules, giving the cell a purple tint so that many gradations between the red and blue are visible. The stain is also valuable in distinguishing the chromophil from the chromophobe adenomas of the pituitary gland and shows that many tumors are mixed, containing both types of granules and cells. Bailie'sstain for the granules in the pituitary cells can also be used afterthese mordants.

COMMENT

A method is described which allows the use of Mallory's differential stains on tissue fixed in 10 per cent formalin. This method is applicable to histology in general but to neuropathology in particular. It also differentiates the three types of cells in the pituitary gland.

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EDITORIAL

A Broader View of Comparative Pathology

Perhaps no other group than laboratory pathologists realizes so keenly the changing concept of cause and effect. One of the principal tenets of medical faith was that there was a uniformity of cause and effect to which those in laboratory medicine have too strictly adhered in practicing their mechanistic philosophy. This theory assumed the identity of morbid causes and the entire similarity of anatomical responses. Such a reasoning begins with the history of medical thought.

It is probable that those keen observers, the internists, who, incidentally, often blaze the trail for us, realized very early that there could not be the same response coming from identic causes by every individual. It is a commentary that bears no extension upon the craft of clinical pathologists that too small a number have admitted this and made their calling flexible.

Perhaps the most conspicuous self-analysis that has ever taken place in this country occurred when the Society recently carried out a critical program on specific therapy. If there be one lesson to be learned from these deliberations, it is that there is a missing link in our understanding and practice of what can and should happen in the vaccine handling of certain cases.

The ordinary acceptance of the term comparative pathology implies finding similar morbid changes in snakes, elephants and men. That such a definition is inadequate is illustrated by many observations. Strychnine does not act the same in birds, dogs and man. The amoebic dysenteries, of spontaneous and experimental character, differ in the principal zoological orders. The incidence of tuberculosis in closely related animals is entirely different. Cerebrospinal nerve tract disease does not occur in lower animals. Anatomical structure, and therefore physiology, may vary in different members of the same genus. Certain

infectious diseases occur only in certain genera and may not be transmissible to another. Species specificity of parasitism is well known.

These and many other examples impel us to wonder if we should think of such pathology as contrastive, not comparative.

Comparative pathology should then be limited to intraspecial occurrences, which would depend upon the facts that perfect, common and mutual anatomy and physiology should exist in every member of the species.

Assuming this to be true, one could with accuracy establish certain tests that would have an absolute or mechanistic value. But, with apologies to Claude Bernard, there is a phase of human pathology that must be described on a constitutional basis, there being no such perfect intraspecial uniformity.

One of the hopes of those who practice laboratory medicine cannot fail to be to establish definite measuring rods for constitutional groups in a comparative sense. The reaction to vaccines in the blood tissue atrophies that may be associated with dermatological response, such as psoriasis, scleroderma and the like, cannot be the same as in the case of a plethoric individual with cardiorenal disease. The blood urea nitrogen output cannot be placed on the same basis in sympatheticatonic persons, as in the stoical manual laborer. The pigmented individual cannot have the same pigment chemistry, and therefore the same protein chemistry, as the blond who has the susceptibility to blood diseases.

The goal then towards which to work in comparative pathology is the establishment of standards closely comparable to clinical standards until clinical material has been so tabulated by mathematical measurements that by a simple formula the value of each one of the variables may be transferred into the value for the other. To what extent the field of laboratory medicine is expected to make diagnoses, and therefore to use pure mechanistic rules, cannot be estimated. But if he who practices it will understand that his experimental lower animals are more likely to present contrastive phenomena and his intra-human examples better considered as giving comparative phenomena, and if he

will realize that each of the individual groups is really sui generis, then will he begin to establish his measuring rods and to contribute to the ever deepening significance of racial variation, the parts of which at the moment fail to stand in mathematical relationship.

This cannot lead to the practice of vitalistic philosophy but it forces greater attention to the species norms, finer divisions into groups, closer study of individual cases, and better analysis of comparative pathology within the intra-human responses.

HERBERT FOX.

SOCIETY NEWS AND NOTICES

Tenth Annual Convention of the American Society of Clinical Pathologists

June 7 to 9, 1931, Philadelphia, Pennsylvania

The American Society of Clinical Pathologists held its Tenth Annual Convention at Philadelphia, June 7–9, 1931. The meeting was one of the most successful ever held, about 100 members registering, and demonstrated that the Society has really become of age.

There were twenty-six papers presented during the scientific sessions and there were ten exhibits. The sessions were well attended, there being as many as 200 in the room at times. An interesting and important feature of the meeting was a symposium of eight papers on vaccine therapy.

The annual banquet was an unusual success and was well attended. The three addresses were delivered by President Kenneth M. Lynch, Dr. B. C. Crowell and Dr. David Riesman. These addresses complimented and supplemented each other in an interesting manner and defined well the field of clinical pathology and its relation to medical sciences. Its importance was clearly pointed out and the qualifications of men practicing the specialty placed on a high plane.

The scientific sessions were held, quite fittingly, in the auditorium of the Philadelphia General Hospital. From the windows of this beautiful structure one could almost see the little old brick building in which Osler did his autopsies and in which many members of the Society obtained their fundamental training in the subject. On view for the members were Dr. Osler's old autopsy table and the original protocols of his examinations. The academic and scientific atmosphere of the building added to the spirit of the meeting.

Important changes in the By-laws were passed which will be found elsewhere in the JOURNAL. The following men were elected to membership: Samuel T. Lindsay, Rochester, N. Y., Roy R. Kracke, Emory University, Georgia, Henry F. Hunt, Danville, Pennsylvania, Marcos Fernan-Nunez, Milwaukee, Wisconsin, Plinn F. Morse, Detroit, Michigan, Hazel R. Prentice, Kalamazoo, Michigan, Frederick O. Zillessen, Fond du Lac, Wisconsin, Benjamin E. Konwaller, Davenport, Iowa, William A. Meyers, Oklahoma City, Oklahoma, and Eric A. Fennel, Honolulu, Hawaii.

The Business meeting was held on Tuesday evening June 9. The following reports were presented and approved:

REPORT OF THE EXECUTIVE COMMITTEE

The Committee wishes to report that the year just closing has been a highly successful one. The affairs of the Association have gone forward in a most satisfactory manner.

The work of the Secretary's office has been carried on efficiently by Dr. Giordano and the Chairman wishes to express his appreciation of the pleasure he has had in working with him. The books of the Secretary have been checked and found in perfect order.

The audit of the accountant shows the financial condition of the Association to be excellent. The assets show a slight increase in spite of the launching of the official JOURNAL Each year has shown a greater financial strength and, though our resources are still small, our condition is sound.

The Committee feels that the Society may be justly proud of the JOURNAL. The material and the mechanical features of the periodical have secured universal approbation. That the Society is able to publish such a JOURNAL with no change in the dues from members is a cause for congratulation. To the Editor and to the Publication Committee we owe a debt of gratitude.

The change in time of meeting was agreed upon as an experiment this year. An expression from the membership as to its continuance is desirable.

A number of changes in the By-Laws have been proposed by this Committee. We trust they will have your thoughtful consideration.

The Committee feels that we have had unusually efficient service from the various committees and wishes to thank them for their labors.

J. H. BLACK,
Chairman.

REPORT OF THE EDITOR-IN-CHIEF

Due largerly to the untiring efforts of Dr. J. A. Kolmer, a contract was entered into with the Williams & Wilkins Company for the publication of the

AMERICAN JOURNAL OF CLINICAL PATHOLOGY. It was decided by the Publication Committee that the JOURNAL should be a bi-monthly publication, beginning with January 1, 1931. Three issues have been published and the fourth is in press.

The response on the part of the membership has been most gratifying. The makers and dealers of scientific equipment have contributed advertising most generously, and the JOURNAL has begun under very favorable conditions.

Certain rules have been published in the JOURNAL governing the type of material to be published and the manner in which it will appear.

The Editor wishes to thank the Society for its coöperation and to request its future support for the JOURNAL.

T. B. MAGATH,
Editor.

THE COMMITTEE ON EXHIBITS

Your Committee on Exhibits begs to express the opinion that no exhibit at this meeting showed a degree of excellence sufficient to warrant the bestowal of a medal on the exhibitor.

It wishes, however, to commend Dr. B. Steinberg for his excellent illustrations on The Pathology and Etiology of Degeneration and Inflammatory Lesions of the Appendix and the Presbyterian Hospital of Philadelphia for the beautiful examples of photography in color.

W. S. THOMAS,
Chairman.

REPORT OF SERVICE BUREAU

The activities of the Service Bureau for the year 1930–31 have continued as in the past. Four members placed their names on registration and six institutions consulted this Bureau for service.

Your committee, in order to be effective in its service, urges that every member who would consider change in location to place their name on file with this committee so that they can be immediately notified as soon as an opening is available. While notices of such openings will be published in the JOURNAL obviously very often too much time elapses from the time of the call to the publication of the notice.

A. S. GIORDANO,
Chairman.

REPORT OF THE RESEARCH COMITTEE

In the absence of the Chairman, Dr. A. G. Foord, Dr. M. Pinson Neal, Acting Chairman, reported that the activities of this Committee have been rather limited because of the failure of most of the members to add their personal cases of blood dyscrasias to the Society's permanent registry. It was stated that only four members contributed case records and slides so far and

it is hoped that many more will be contributing in the future. The subjects of agranulocytosis, acute leukemia, blood dyscrasias following arsphenamine therapy and pernicious anemia like syndromes were chosen because of universal interest in these conditions and because of the ease of collection.

The Committee recommended the Huppert-Nakayama test for the presence of bilirubin in urine, based upon favorable reports received.

The Committee recommended that the hematologic collection be continued for the next few years and is also desirous of receiving comments for future studies.

The Committee again made a plea to the Executive Committee to set up more definite rules for making the annual Ward Burdick award. The award this year was granted to Dr. W. G. Exton.

M. PINSON NEAL,
Acting Chairman.

REPORT OF THE PUBLICATION COMMITTEE

The Publication Committee reported that the book on Approved Laboratory Technique, prepared under the auspices of the Society, is finished and is expected to appear from the press in August.

J. A. KOLMER,
Chairman.

REPORT OF THE BOARD OF REGISTRY

The Board of Registry submits a very extensive report of their activities and also submits a financial statement which is referred to the Executive Committee for approval.

They have approved 6 universities and colleges that give courses in medical technology, 5 universities hospital laboratories, 14 hospital laboratories and 6 hospital laboratories conditionally.

Attached to this report is a very extensive investigation by Dr. K. Ikeda pertaining to institutions available for training of technicians and medical technologists.

P. HILLKOWITZ
Chairman.

REPORT OF THE SECRETARY-TREASURER

The year of 1930–31 marks an important step in the history of the American Society of Clinical Pathologists—namely, the publication of the official JOURNAL and the completion of the Book on approved laboratory methods sponsored by your Society. For these accomplishments the Society owes a debt of gratitude to the untiring efforts of Dr. John A. Kolmer for bringing about the arrangements with the publishers; to Dr. T. B. Magath as Editor-in-Chief of the JOURNAL belongs the credit for the high standard upon which the JOURNAL

is run. This office carries many responsibilities and there is a great deal of labor in editing material submitted for publication.

The publication of the JOURNAL without increasing the membership dues has been made possible by greatly curtailing office expenses. For the present the Secretary's office is conducted with only a part time stenographic service and so far the rental of space has been donated.

For the good of the Society it is imperative that we create a reserve fund for future development of our activities. This can be accomplished only by coöperation of our entire membership in eliminating all unnecessary correspondence. This year we have requested that members make their own reservations with Hotels. Since the publication of our JOURNAL, circular letters have been reduced to a minimum. I, therefore, urge you to read carefully the column on Society news and notices and hope that every member contribute to this by writing directly to the Editor-in-Chief.

Since your Society is obligated to pay $5.00 of its dues for the JOURNAL, it is obvious that no member should expect to receive the JOURNAL without meeting his financial obligation. If you are not receiving the JOURNAL or have changed address, please notify your Secretary's office at once.

There are at present 376 active members. During the year 2 members resigned because of ill health and 4 were lost to the Society because of death.

The Secretary wishes to thank the Committee chairmen for their splendid work and coöperation. All the committees have functioned independently and due credit should be given them for their accomplishments. This is particularly ture of the Committee on Local Arrangements. They have done their work efficiently and deserve thanks from our membership.

The following financial report, as approved by the Executive Committee, shows the standing of the Society at the close of the fiscal year, May 31, 1931:

STATEMENT OF RECEIPTS AND DISBURSEMENTS FROM JUNE 1, 1930 TO MAY 19, 1931

Balance in bank, May 31, 1930 (Goldberg, Fox & Co. Report)		$3,371.40
Receipts:		
Initiation Fees	$425.00	
Membership Dues	3,410.00	
Technicians Registry	1,530.28	
Convention Expense-Refund	484.96	
Commercial Exhibits	180.00	
Lantern Sold	30.00	
Telephone Refund	2.19	
Miscellaneous	3.50	
Collections on Checks returned by banks	31.75	
Total receipts		6,097.68
Total cash to be accounted for		$9,469.08

Disbursements:

Initiation Fees Refunded		$195.00
Membership Dues Refunded		10.00
Technicians Registry		1,034.50
Convention Expense		1,209.39
Salary—Marie Boes	$195.00	
—R. H. Broderick	100.00	
—Alice Gracy	250.00	
—Stenographic Service	19.25	564.25
Office Rent		25.00
Office Supplies		24.95
Telephone		6.82
Postage		81.80
Printing and Multigraphing		332.91
Goldberg, Fox & Co. Audit		37.50
Freight and Cartage		111.34
Miscellaneous		26.29
Williams & Wilkins Subscriptions		1,780.00
Uncollected Checks returned by Banks		41.75
Total disbursements		$5,481.50
Balance in bank, May 19, 1931		$3,987.58

REPORT OF THE NECROLOGY COMMITTEE

In Memoriam

Take them, O Father, in immortal trust!
Ashes to ashes, dust to kindred dust,
Till the last angel rolls the stone away,
And a new morning brings eternal day!

Oliver Wendell Holmes, M.D.

During the past year the American Society of Clinical Pathologists has lost through death four of its members.

We wish to express to their families our sincere sympathy and our appreciation of the valuable services our late colleagues rendered to the public and medical profession in their efforts in the field of clinical pathology.

Edward Fenton Cooke, Houston, Texas. Born in Oldham, England, August 24, 1875. Common and private school education leading to Fort Worth School of Medicine where he graduated in 1897. Licensed under the Act of 1907 in Texas. He practiced at Houston, then at Forreston, Texas, and then returned to Houston where he has been since 1911.

Died January 8, 1931, age 55, of chronic myocarditis.

Dr. Cooke was a member of the American Medical Association, Society of American Bacteriologists, South Texas Medical Association. He was secretary and treasurer of South Texas Medical Association for six years and in October of 1913 was chosen as President of that Association. He was an active member in the Texas Society of Clinical Pathologists and in the affairs of the American Society of Clinical Pathologists.

Frank Riecker Lyne, Chagrin Falls, Ohio. Born in Stockport, Ohio. Graduated Lowell, Ohio, High School, 1914. A.B. Marietta College, 1917. Graduated Western Reserve University School of Medicine, 1922. Licensed in Ohio, 1922.

Died in Chagrin Falls, June 19, 1930 of a bullet wound.

Dr. Lyne was a member of the Ohio State Medical Association and member of the American Medical Association, Society American Bacteriologists; was on staff of Fairview Park Hospital, Cleveland, Ohio, as pathologist. He was the son of Dr. George L. Lyne of Medina, former County Health Commissioner.

Harold Gustavus Palmer, Philadelphia, Pa. Born in Chicopee, Mass., November 5, 1873. Graduated from University of Pennsylvania School of Medicine in 1895. Licensed in Philadelphia 1896 and in Pennsylvania 1926. Practised in Pittsburgh, Pa., and Providence, R. I. 1915–1918. Was on the staff of St. Elizabeth's Hospital, Washington, D. C., in 1924; St. Agnes Hospital, Philadelphia at his demise.

Died in Philadelphia, American Oncologic Hospital, March 15, 1930, bronchopneumonia. Age 57 years.

Fellow of the American Medical Association and Rhode Island Medical Society.

James Roe Snyder, Sacramento, California. Born in Scriba, New York, November 2, 1888. Graduated from Chicoa, California, High School. Graduated from Syracuse University College of Medicine 1912.

Fellow of American Medical Association; was in City Laboratory in Sacramento, California at time of his death.

J. J. Moore,
Chairman.

The Nominating Committee presented the following names:

President-elect: WALTER M. SIMPSON
Vice-President: C. J. BUCHER
Executive Committee: K. M. LYNCH
A. J. FOORD
Board of Censors: NATHAN ROSENTHAL
F. M. JOHNS
Board of Registry of Technicians: W. E. KING
ASHER YAGUDA

The above candidates were unanimously elected. The members retiring from the committees are:

Executive Committee: J. A. KOLMER
A. H. SANFORD
Board of Censors: ERNST SCOTT
B. W. RHAMY
Board of Registry of Technicians: A. G. FOORD
C. Y. WHITE

PAST PRESIDENTS

1922–3	Dr. Philip Hillkowitz	Denver, Colorado
1923–4	Dr. Wm. Carpenter MacCarty	Rochester, Minnesota
1924–5	Dr. John A. Kolmer	Philadelphia, Pa.
1925–6	Dr. Frederic E. Sondern	New York, N. Y.
1926–7	Dr. Wm. G. Exton	Newark, New Jersey
1927–8	Dr. A. H. Sanford	Rochester, Minnesota
1928–9	Dr. F. W. Hartman	Detroit, Michigan
1929–30	Dr. J. H. Black	Dallas, Texas
1930–1	Dr. K. M. Lynch	Charleston, S. C.

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FINKELSTEIN, MANLY	1185 Wolseley Ave., Winnipeg, Canada
*GARBER, C. Z.	Peking Union Medical College, Peking, China

KELLY, FRANK L.....U. S. N., First Brigade U. S. Marines, Cape Haitien, Republic of Haiti
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*SHEARD, CHARLES..Rochester, Minn.
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SHEPPE, WM. M.....Wheeling, W. Va.
SHILLING, E. R.....Columbus, Ohio
SHIRMER, EMILIE C...Brooklyn, N. Y.
SICKEL, GEORGE B.....Chester, Pa.
SIMPSON, JOHN C.....Norristown, Pa.
SIMPSON, WALTER M....Dayton, Ohio
SMITH, ESMONDE B...Brooklyn, N. Y.
SMITH, WILLIAM A....Memphis, Tenn.
SONDERN, FRED. E...New York, N. Y.
SPAETH, WM. L. C...Philadelphia, Pa.
SPITZ, HERMAN.....Nashville, Tenn.
SPOHR, CARL L.....Columbus, Ohio
STAFFORD, C. M.....Detroit, Mich.
STAINES, MINNIE E.
Colorado Springs, Colo.
STANGL, FRED H.....St. Cloud, Minn.
STARRY, A. C.....Sioux City, Iowa
STEINBERG, BERNHARD...Toledo, Ohio
STEWART, HENRY.....Gettysburg, Pa.
ST. GEORGE, A. V...New York, N. Y.
STIER, ROBT. F. E.....Spokane, Wash.
STILLMAN, RALPH G.New York, N. Y.
**STITT, EDW. R...Washington, D. C.
ST. JOHN, E. Q.....Philadelphia, Pa.
STONE, MURRAY C....Springfield, Mo.
STONE, W. B.....Schenectady, N. Y.
STOUT B. F.....San Antonio, Texas
STOWE, W. P.....San Francisco, Calif.
SULLIVAN, HELEN C.....Denver, Colo.
SWAN, MARY H.....Chicago, Ill.
SWEANY, HENRY C.....Chicago, Ill.
TERRELL, T. C...Forth Worth, Texas
TERRY, BENJ. T.....Rochester, Minn.
THALHIMER, WILLIAM.....Chicago, Ill.
THARINGER, E. L.....Milwaukee, Wis.
THOMAS, W. S..Clifton Springs, N. Y.
THOMPSON, H. E.....Bangor, Me.

THOMSON, W. F.....Beaumont, Texas
THRO, WM. C.....New York, N. Y.
TODD, LESTER C.....Charlotte, N. C.
TRIMBLE, WM. K....Kansas City, Mo.
*TURLEY, LOUIS A.....Norman, Okla.
TURNER, GEO.....El Paso, Texas
VAN ATTA, J. R...Albuquerque, N. M.
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VENABLE, D. R....Wichita Falls, Tex.
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VOLLMER, MAUD J.....Moline, Illinois
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Jersey City, N. J.
WADDELL, C. W....Fairmount, W. Va.
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WALKER, THAD...Grosse Pointe, Mich.
WALKER, THOS. F..Great Falls, Mont.
WARREN, MORTIMER....Portland, Me.
WATTERS, WM. HENRY..Boston, Mass.
**WELCH, WILLIAM H. Baltimore, Md.
WELLBROCK, W. L. A. Rochester, Minn.
WESCOTT, A. M.....Newburgh, N. Y.
WEST, O. J.....Seattle, Wash.
WEST, P. C.....Seattle, Wash.
WHITE, C. Y.....Philadelphia, Pa.
WHITE, E. T.....Greenville, Miss.
WHITE, G. H., JR.....Baltimore, Md.
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WOODWARD, L. R....Mason City, Iowa
WURTZ, JOHN G.....Wilkinsburg, Pa.
*WYANDT, MISS HELEN.Omaha, Nebr.
YAJUDA, ASHER.....Newark, N. J.
YOUMANS, IVA C.....Miami, Fla.
ZBINDEN, THEODORE.....Toledo, Ohio
ZILLESSEN, F. O..Easton, Pennsylvania

Dr. Kenneth M. Lynch, Professor of Pathology at the Medical College of the State of South Carolina, received the honorary degree of Doctor of Laws from the University of South Carolina at the commencement exercises of the University on June 10.

Wanted: A pathologist in the Department of Pathology of a southern Medical School. Maximum salary $4500.00. Communicate with Secretary.

If a man claiming to be "Doctor" W. W. Haid applies for work, communicate with Dr. R. G. Owen, 507 Stroh Building, Detroit, Michigan, who will be glad to furnish his record.